HYPERTENSION GUIDELINES

ROADMAP OR ABSENTWAY

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What is Evidence Based Practice?

Conscientious, explicit & judicious use of best current evidence in making decisions of care for clients

NEW HYPERTENSION GUIDELINES, 2015

- JNC-8 Panel: JAMA 2014; 311:507
- JNC-8 Minority Panelists: Ann Int Med 2014; 160:449
- AHA/ACC/CDC Advisory: J Am Coll Card 2014; 63:1230
- Am Society of Hypertension: J Clin Hypertens 2014; 16:14
- Canadian Hypertension Education Program: Can J Card 2014; 30:485
- Joint British Societies 3: Heart 2014; 100 (Suppl 2):1
- ESH/ESC: J Hypertens 2013; 31:1281
- Japanese Society of Hypertension: Hypertension Res 2014; 37:253
- KDIGO Blood Pressure Work Group: Kid Int 2012; Suppl 2
- American Diabetes Association: Diabetes Care 2015; 38 (Suppl 1):S49
- Taiwan Hypertension Society: J Clin Med Assoc; on-line 12/26/2014

HYPERTENSION: VERY TREATABLE

Meta-analysis: 68 RCTs; 245,885 pts; 4.3y FU

- ↓ SBP/DBP by 10/5 mm Hg for 5y:

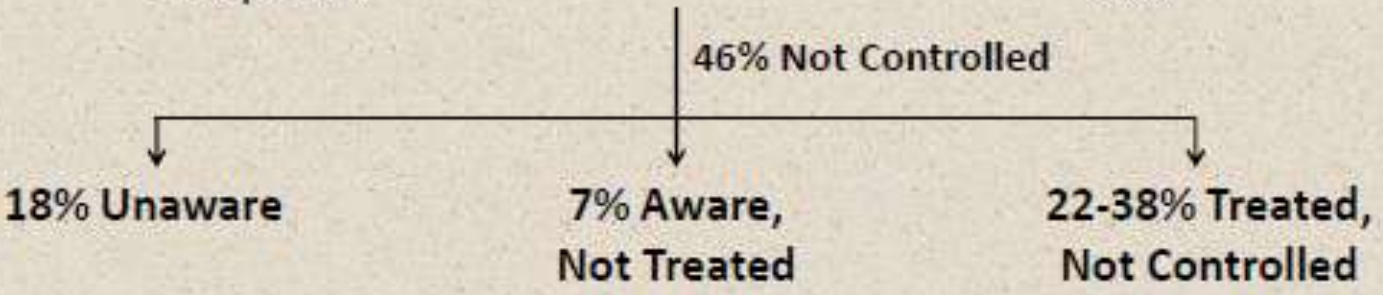
Complication	% Risk Reduction	NNT x 5y
CVD events	25%	36
Heart failure	43%	73
Stroke	36%	58
MI	16%	160
Mortality	11%	125
Dementia	?	?

J Hypertension 2014; 32:2285

HTN CONTROL: IMPROVING, BUT STILL UNACCEPTABLE

NHANES:

	1980	2012
Aware	51%	83%
Treated	31%	77%
Controlled (< 140/90)	10%	54%
• Blacks		41%
• Hispanics		34%



Circulation 2015; 131:e86 JACC 2012; 60:599 JAMA 2010; 303:204

JNC-8 Recommendations

	BP thresholds	Goals
✓ *Recommendation* **1** *(Strong recommendation)* — **General population ≥60 years**	**SBP ≥150 mm Hg or DBP ≥90 mm Hg**	**SBP <150 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **2** *(Strong recommendation)* — **General population <60 years**	**DBP ≥90 mm Hg**	**DBP <90 mm Hg**
✓ *Recommendation* **3** *(Expert opinion)* — **General population <60 years**	**SBP ≥140 mm Hg**	**SBP <140 mm Hg**

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

Recommendations

	BP thresholds	Goals
✓ *Recommendation* **4** *(Expert opinion)*		
Population with CKD ≥18 years	**SBP ≥140 mm Hg or DBP ≥90 mm Hg**	**SBP <140 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **5** *(Expert opinion)*		
Population with diabetes ≥18 years	**SBP ≥140 mm Hg or DBP ≥90 mm Hg**	**SBP <140 mm Hg and DBP <90 mm Hg**
✓ *Recommendation* **6** *(Moderate recommendation)*		
General nonblack population *(with diabetes)*	**Initial treatment**	
	Thiazide-type diuretic, CCB, ACEI, Or ARB.	

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

Recommendations

✓ *Recommendation* **7**

(Moderate recommendation)

General *(with diabetes)* black population

Initial treatments

Thiazide-type diuretic, or calcium channel blocker (CCB)

✓ *Recommendation* **8**

(Moderate recommendation)

Population with CKD ≥18 years

Initial or add-on treatments

ACEI, Or ARB

✓ *Recommendation* **9**

(Expert opinion)

Goal BP not reached within a month of treatment

Non control strategies

Increase the dose of the initial drug, or add a second drug *(from the list provided)*

Goal BP not reached with 2 drugs

Add and titrate a third drug *(from the same list)*
Do not use an ACEI and an ARB together in the same patient

JAMA. doi:10.1001/jama.2013.284427. Published online December 18, 2013.

HYPERTENSION GUIDELINES 2015: NOT SO MUCH CLARITY

"Hypertension guidelines – clear as mud."

TheHeart.org

"Why doctors are fighting over blood pressure guidelines."

Time, 2014

"The multitude of guidelines from respected professional bodies and individuals have caused needless confusion bordering on chaos."

Editorial, J Clin Hypertens 2014; 16:251

ESSENTIAL MESSAGES FROM ESC GUIDELINES

Committee for Practice Guidelines
To improve the quality of clinical practice and patient care in Europe

European Society of Hypertension

Hypertension

GUIDELINES FOR THE MANAGEMENT OF ARTERIAL HYPERTENSION

For more information
www.escardio.org/guidelines

1 - Total cardiovascular risk stratification

- *Decisions on management of the hypertensive patient depend on the initial level of total CV risk.*
- *The stratification of total CV risk in different categories is based on BP category, CV risk factors, asymptomatic OD and presence of diabetes, symptomatic CV disease or CKD.*
- *The classification in low, moderate, high and very risk refers to the 10-year risk of CV mortality as defined in 2012 Joint CVD Prevention Guidelines.*

Figure 1 Stratification of total CV risk in categories of low, moderate, high and very high risk according to SBP and DBP and prevalence of RFs, asymptomatic OD, diabetes, CKD stage or symptomatic CVD. Subjects with a high normal office but a raised out-of-office BP (masked hypertension) have a CV risk in the hypertension range. Subjects with a high office BP but normal out-of-office BP (white-coat hypertension), particularly if there is no diabetes, OD, CVD or CKD, have lower risk than sustained hypertension for the same office BP.

Other risk factors, asymptomatic organ damage, or disease	Blood Pressure (mmHg)			
	High normal SBP 130–139 or DBP 85–89	Grade 1 HT SBP 140–159 or DBP 90–99	Grade 2 HT SBP 160–179 or DBP 100–109	Grade 3 HT SBP ≥180 or DBP ≥110
No other RF		Low risk	Moderate risk	High risk
1–2 RF	Low risk	Moderate risk	Moderate to high risk	High risk
≥3 RF	Low to Moderate risk	Moderate to high risk	High Risk	High risk
OD, CKD stage 3 or diabetes	Moderate to high risk	High risk	High risk	High to very high risk
Symptomatic CVD, CKD stage ≥4 or diabetes with OD/RFs	Very high risk	Very high risk	Very high risk	Very high risk

BP = blood pressure; CV = cardiovascular; CVD = cardiovascular disease; CKD = chronic kidney disease; DBP = diastolic blood pressure; HT = hypertension; OD = organ damage; RF = risk factor; SBP = systolic blood pressure.

2 - Diagnostic evaluation

- *Initial evaluation of a patient with hypertension:*
  1) confirm the diagnosis of hypertension;
  2) detect causes of secondary hypertension; and
  3) assess CV risk, OD & other clinical conditions.

- *This calls for BP measurement, medical history including family history, physical examination, lab investigations & further diagnostic tests.*

- *Some of the investigations are needed in all patients, others only in specific patient groups.*

2a. Blood pressure measurement

- *Office blood pressure; Conventional office BP measurement by use of a validated device is the gold standard for screening, diagnosis and management of hypertension.*
- *Hypertension is defined as systolic BP ≥140 mmHg and/or diastolic BP ≥90 mmHg.*
- *Diagnosis of hypertension should be based on at least two BP measurements in the sitting position*

BP MEASUREMENT: KEY TECHNIQUES

	△ BP (mm Hg) if not done
Rest ≥ 5 min, quiet	↑ **12/6**
Seated, back supported	↑ 6/8
Cuff at midsternal level	↑ ↓ 2/inch
Correct cuff size	↑ **6-18/4-13 if too small**
	↓ 7/5 if too large
Bladder center over artery	↑ 3-5/2-3
Deflate 2 mm Hg/sec	↓ SBP/↑ DBP
No talking during measurement	↑ 17/13
If initial BP > goal BP:	**1st reading higher**
3 readings, 1 min apart	• "Alerting response"
Discard 1st, average last 2	• Reclassify 18-34% as normotensive

- **Requires 8-11 minutes!**

J Clin Hypertens 2012;14:751 Hypertension 2005; 45:142 J Gen Int Med 2012; 27:623 J Hypertens 2005; 23:697 Can J Card 2014; 30:485

Out-of-office BP

- *Out-of-office BP, assessed by ambulatory or home BP monitoring, is an important adjunct to office BP. The prediction of CV events is significantly better with out-of-office BP than with office BP.*

- *Prognosis is better in white-coat hypertension than in sustained hypertension and appears to be similar to that in true normotension.*

- *The incidence of CV events is about two times higher in masked hypertension than in true normotension and similar to the incidence in sustained hypertension.*

HOW TO DIAGNOSE HYPERTENSION IN 2015?

Guideline	Gold Standard to Dx HTN
ASH/ISH 2014;	OBPM ≥ 2 visits
ESH 2013	• ABPM/HBPM if suspect WCH, "borderline" BP, variable BP
CHEP 2015	• OBPM x 2 visits if TOD, CKD, DM, or BP ≥ 180/110 • Confirm with ABPM > HBPM
Taiwan 2015; FSH 2013	• OBPM x 2 visits if TOD • Confirm Dx in all others with ABPM or HBPM
NICE (UK) 2011; USPSTF 2015	Confirm with ABPM > HBPM

J Chi Med Assoc 2015; online 12/26/2014

J Hypertens 2014; 32:3 Fundam Clin Pharm 2014; 28:1 Eur Heart J 2013; 34:2159 BMJ 2011; 343:d4891 Can J Card 2014; 30 485 USPSTF website

- *Cut-offs for the definition of hypertension are: 130/80 mmHg for 24-h BP, 135/85 mmHg for daytime ambulatory BP and home BP and 120/70 mmHg for night-time BP.*

- *Major indications for out-of-office BP are suspicion of white-coat, masked or nocturnal hypertension, suspected hypotension, considerable variability of office BP and treatment-resistant hypertension.*

TARGET BP 2014: STILL NO CONSENSUS!

Guideline	General Population	Age ≥ 80y	CKD	DM
ASH 2014	< 140/90	< 150/90	< 140/90	< 140/90
ACC/AHA 2014	< 140/90	< 150/90	< 140/90	< 140/90
CHEP 2015, JBS3 2014	< 140/90*	**< 150/90 (Rx if ≥ 160**)**	< 140/90	**< 130/80**
JNC-8 2014				
• Majority:				
- Age < 60	< 140/90	---	< 140/90	< 140/90
- Age ≥ 60	**< 150/90*** **	< 150/90		
• Minority:	< 140/90	< 150/90		
ADA 2015	---	---	---	**< 140/90****
NKF/KDIGO 2012	---	< 150/90?	< 140/90	< 140/90
• ACR ≥ 30	---	?	**< 130/80**	**< 130/80**

*< 160/100 if no TOD or CVD risk factors

** If no TOD or DM; otherwise Rx if ≥ 140/90

*** No down-titration needed if tolerate < 140/90

**** < 130 if ↑ stroke risk

2b. Cardiovascular risk factors

- *Total, LDL and HDL cholesterol, and fasting triglycerides and glucose are considered routine tests in all hypertensive patients.*

2c. Search for secondary hypertension.

- *All patients should undergo simple screening tests for 2ndry hypertension, including clinical history, P.E. & lab. Inv., & a focused search should be undertaken when indicated.*

2d. Search for asymp. OD & symp. Disease

- ***Heart:*** *ECG is recommended in all hypertensive patients; additional tests (echo, exercise testing, Holter monitoring) should be considered based on history, physical examination and ECG findings.*

- ***Arteries:*** carotid and peripheral ultrasound, pulse wave velocity and ankle-brachial index should be considered as additional tests if indicated.

- ***Kidney:*** measurement of serum creatinine and eGFR, urinary protein and microalbuminuria are recommended in all hypertensive patients.

3 - Treatment approach

3a. Lifestyle changes

- *Appropriate lifestyle changes are the cornerstone for the prevention of hypertension and are also important for its treatment. Following lifestyle measures are recommended:*

- *Salt restriction to 5-6 g/day.*
- *Moderation of alcohol consumption (<20-30 g of ethanol per day in men and <10-20 g in women).*
- *Increased consumption of vegetables, fruits and low-fat dairy products.*
- *Reduction of weight to BMI of 25 kg/m2.*
- *Regular exercise (≥30 min of moderate dynamic exercise on 5-7 days per week)*
- *Smoking cessation*

DOES ↓ DIETARY Na REDUCE CVD?

(IT CLEARLY LOWERS BP!)

↓

Minimal RCT data:

- Require 30,000 pts x 5y

↓

Cohort data: 31 analyses of 285,530 pts

- Substantial methodologic deficiencies in most

13 studies → ↓ CVD

8 studies → ↑ CVD

2 studies → J-curve

8 studies → No effect

Post-hoc 15y FU of TOHP: 2275 pts

> 3600 vs < 2300 mg/d → low Na ↓ CVD by 32%

Circulation 2014; 129:1173 Circulation 2014; 129:981 IOM, 2013

Na RESTRICTION: CURRENT GUIDELINES

	Na (mg/d)
AHA, 2012/2014	< 1500
WHO, 2012	< 2000
CHEP, 2015	< 2000
DHSS, 2010	< 2300
IOM, 2013	2300
Graudal, et al 2014	2600-4900

www.hypertension.ca Circulation 2014; 129:1173 Am J Hypertens 2014; 27:282; 1143; 1138

3b. Initiation of antihypertensive treatment.

- *Prompt initiation of antihypertensive drug is recommended in patients at high or very high CV risk.*

- *Antihypertensive drugs should be considered in patients at moderate or low risk when BP remains >140/90 mmHg after, respectively, several weeks or months of appropriate lifestyle measures, or in case of persistently elevated out-of-office BP.*

- *In elderly patients drug treatment is recommended when systolic BP is ≥160 mmHg, or ≥140 mmHg if younger than 80 years and treatment is well tolerated.*

- *It is not recommended to initiate antihypertensive treatment at high normal BP and in younger patients with isolated systolic hypertension.*

WHEN TO INITIATE HTN TREATMENT?

Support for ≥ 150/90 For Age ≥ 60y, No CKD/DM

No definitive RCT for 140-149

Cochrane 2012 meta-analysis:

- No ↓ CVD events for 140-149

Marginal benefits/side effects

Support for ≥ 140/90 For Age ≥ 60y, No CKD/DM

One RCT, CARDIO-SIS 2014 meta-analysis:

– ↓ Stroke, CHD for 140-149

Epidemiologic data:

↑ CVD begins at SBP=90

JAMA 2014; 311:507 JACC 2014; 64:394 Heart 2014; 100:317
J Hypertens 2014; 32:2296 Cochrane Syst Rev 2012; 8:CD006742

3c. Blood pressure goals

- ***Systolic BP;*** *A systolic BP goal of <140 mmHg is recommended in all hypertensive patients, with few exceptions:*

In elderly hypertensive patients less than 80 years old there is solid evidence to reduce systolic BP to between 150 and 140 mmHg, but a goal of <140 mmHg may be considered in fit elderly.

In individuals older than 80 years it is recommended to reduce BP to between 150 and 140 mmHg if they are in good physical and mental condition.

- ***Diastolic BP;*** *A diastolic BP of <90 mmHg is always recommended, except in patients with diabetes, in whom values <85 mmHg are recommended.*

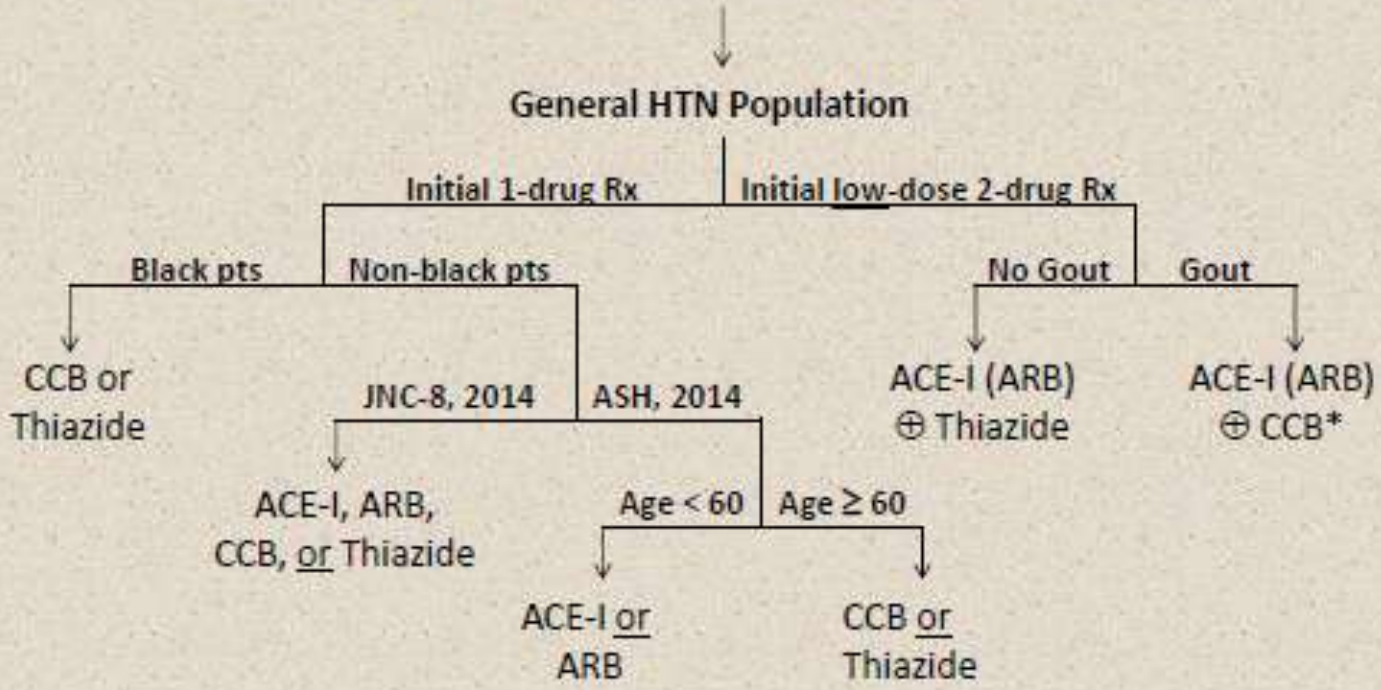
3d. Choice of antihypertensive drugs

- *Diuretics, beta-blockers, calcium antagonists, ACEIs & ARBs are all suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination therapy.*

- *Some agents should be considered as the preferential choice in specific conditions, such as coronary heart disease, heart failure, diabetes or renal dysfunction.*

- *Initiation of antihypertensive therapy with two-drug combination may be considered in patients with markedly high baseline BP of at high CV risk. Among the many possible combinations, some are considered more suitable than others.*

SELECTING INITIAL PHARMACOLOGIC THERAPY



*Consider this Rx if high CVD risk (ACCOMPLISH RCT, 2008)

J Hum Hypertens 2015; 29:22 JAMA 2014; 311:507 J Hypertens 2014; 32:3 J Clin Hypertens 2013; 15:874

4 - Treatment strategies in special conditions

4a. White-coat and masked hypertension

- *In white-coat hypertensives without additional risk factors, therapeutic intervention is limited to lifestyle changes and close follow-up is warranted. In case of higher CV risk, drug treatment may be considered.*

- *In masked hypertension, both lifestyle measures and drug treatment should be considered because of the high CV risk.*

4b. Elderly

- *When antihypertensive therapy is indicated as described in section 3b, all antihypertensive agents can be used, although diuretics and calcium antagonists may be preferred in ISH.*

4c. Pregnancy

- *Drug treatment is recommended in severe HTN in pregnancy (BP >160/110 mmHg), and may be considered in case of persistent BP ≥150/95 mmHg, and in those with BP ≥140/90 mmHg in the presence of asymptomatic OD or symptoms.*
- *Methyldopa, labetalol and nifedipine should be considered preferential antihypertensive drugs in pregnancy. RAAS Blockers should be avoided*

4d. Diabetes

- *It is recommended to start drug treatment when systolic BP is ≥140 mmHg. The BP target is <140/85 mmHg.*

- *All classes of antihypertensive drugs can be used, though RAAS blockers may be preferred, especially in the presence of proteinuria or microalbuminuria, but simultaneous administration of two RAAS blockers should be avoided.*

4e. Nephropathy

- *It is recommended to start drug treatment when systolic BP is ≥140 mmHg, targeting <140 mmHg.*

- *A target of <130 mmHg may be considered in case of overt proteinuria, and blockers of the renin- angiotensin system (though not in combination) are indicated in the presence of proteinuria or microalbuminuria.*

4f. Cerebrovascular disease

- *It is not recommended to intervene with BP-lowering therapy during the first week after acute stroke, although clinical judgement should be used in the face of very high systolic BP values.*

- *Antihypertensive treatment is recommended in hypertensive patients with a history of stroke or TIA when systolic BP is ≥140 mmHg, targeting <140 mmHg.*

- *All drug regimens are recommended in these patients, provided that BP is effectively reduced.*

4g. Heart disease

Coronary heart disease

- *It is recommended to start drug treatment when systolic BP is ≥140 mmHg, and all agents can be used, targeting <140 mmHg.*

- *BB are recommended in case of recent MI, and BB and CCB in patients with angina pectoris.*

Heart failure

- *Diuretics, BB, ACEIs, ARBs &/or Aldost. antagonist are recommended in patients with HF or severe LVD.*
- *There is no evidence that antihypertensive therapy per se or any particular drug is beneficial in case of preserved ejection fraction.*
- *Lowering of systolic BP to around 140 mmHg should be considered in all of these patients.*

Left ventricular hypertrophy

- *Antihypertensive therapy is recommended, and initiation with one of the agents that have shown greater ability to regress LVH should be considered, i.e. ACEIs, ARBs & CCB*

4h. Resistant hypertension

- *In case of true treatment-resistant hypertension, addition of a mineralocorticoid receptor antagonist, amiloride, and/or the alpha-blocker doxazocin should be considered.*

- *In case of ineffectiveness of drug treatment invasive procedures such as renal denervation and baroreceptor stimulation may be considered.*

Resistant Hypertension On ACE-I (ARB) ⊕ Chlorthalidone ⊕ Amlodipine

✓ eGFR/K+

≥ 50 ml/min and < 4.5 mEq/L

Yes

Spironolactone,

12.5 → 25 mg/d

q 4 wks, prn

- ✓ K+/creatinine at 1 and 4 wks

eGFR < 50 ml/min or K+ ≥ 4.5 mEq/L

HR ≥ 84-90/min?

Yes

Carvedilol 25→50 mg bid or Metoprolol 50→100 mg bid

q 2-4 wks, prn

- Monitor HR

eGFR < 50 ml/min or K+ > 4.5 and HR < 84-90/min

Doxazosin hs

2 → 4 → 8 mg

q 2-4 wks prn

Diltiazem ER

180 → 240 mg/d

q 2-4 wks, prn

- ✓ for edema

5 - Treatment of associated risk factors

- *It is recommended to use statin therapy in hypertensive patients at moderate to high CV risk, targeting an LDL cholesterol value <115 mg/dL. When overt CHD is present, it is recommended to administer statin therapy to achieve LDL cholesterol levels <70 mg/dL.*

- *In hypertensive patients with diabetes, a HbA1c target of <7.0% is recommended with antidiabetic treatment. In more fragile elderly patients with a longer diabetes duration, more comorbidities and at high risk, treatment to a HbA1c target of <7.5–8.0% should be considered.*

- *Antiplatelet therapy, in particular low-dose aspirin, is recommended in hypertensive patients with previous CV events.*

- *Aspirin should also be considered in hypertensive patients with reduced renal function or at high CV risk, provided that BP is well controlled.*

- *Aspirin is not recommended for CV prevention in low-moderate risk hypertensive patients, in whom absolute benefit and harm are equivalent.*

6 - Follow-up and improvement of BP control

- *Individuals with high normal BP or white-coat hypertension, even in untreated, should be scheduled for regular follow-up, at least annually, to measure office and out-of-office BP, to check the CV risk profile and to reinforce recommendations on lifestyle changes.*

- *After initiation of antihypertensive drug therapy in patients with hypertension, the patient should be seen at 2- to 4-week intervals to evaluate the effects on BP and to assess possible side-effects.*

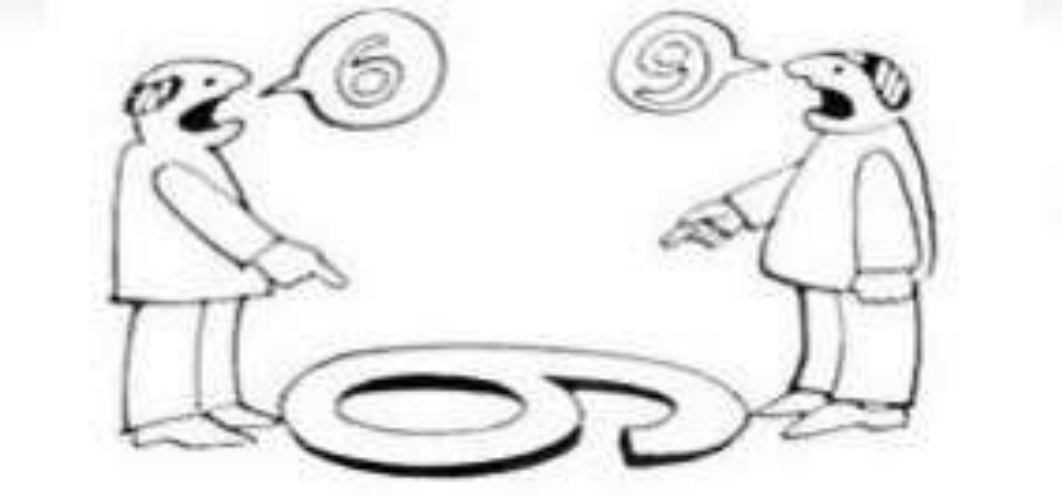
- *Once the target BP is reached, a visit interval of a few months is reasonable. Depending on the local organization of health resources, many of the later visits may be performed by non-physician health care workers, such as nurses. For stable patients, home BP monitoring and electronic communication with the physician provides acceptable alternative.*

- *It is advisable to assess risk factors & asymptomatic organ damage at least every 2 years.*

- *Uncontrolled BP should always lead to a search for the cause(s), such as poor adherence, persistent white-coat effect or use of BP-raising substances. Appropriate actions should be taken for better BP control, avoiding physician inertia.*

Evidence vs Judgment

You can´t have it both ways !



As much evidence as possible, as much judgement as needed.

UP TO DATE VER. 33 TOPIC No.7169

- *Studies of antihypertensive therapy in proteinuric nondiabetic CKD have focused on two areas:*

  short-term reduction in protein excretion; and

  long-term protection against progressive kidney disease.

- *Data are limited on nonproteinuric CKD, defined as CKD associated with urine protein excretion <0.5-1g/day.*

Renoprotective Effect of RAAS Blockade in Patients With Predialysis Advanced CKD, Hypertension, and Anemia

Hsu TW, Liu JS, Hung SC, et al.

JAMA Intern Med 2014;174:347-354.

Study Question: ***How effective and safe is ACEI or ARB use for advanced predialysis CKD in patients with hypertension and anemia?***

- *This was a prospective cohort study in Taiwan. From January 1, 2000, through June 30, 2009, the investigators selected 28,497 hypertensive adult patients with CKD. Serum creatinine levels were >6 mg/dl, hematocrit levels were <28%, and patients were treated with ESAs.*

- *There were users (n = 14,117) and nonusers (n = 14,380) of ACEIs/ARBs.*

- *The authors used Cox proportional hazards regression models to estimate HRs for start of long-term dialysis and all-cause mortality for ACEI/ARB users versus nonusers.*

Results

- *In a median follow-up of 7 months, 20,152 patients (70.7%) required long-term HD and 5,696 (20.0%) died before progression to ESRD requiring dialysis.*
- *Use of ACEIs/ARBs was associated with a lower risk for long-term HD (HR, 0.94; 95% CI, 0.91-0.97) and the composite outcome of long-term dialysis or death (HR, 0.94; 95% CI, 0.92-0.97).*
- *The renal benefit of ACEI/ARB was consistent across patient subgroups, as was ACEI/ARB monotherapy.*
- *Compared with nonusers, the ACEI/ARB users had a higher hyperkalemia-associated hospitalization rate, but the risk of predialysis mortality caused by hyperkalemia was nill (HR,1.03; 95% CI,0.92-1.16).*

Conclusions

- *The authors concluded that patients with stable hypertension and advanced CKD who receive therapy with ACEIs/ARBs exhibit an association with lower risk for long-term dialysis or death by 6%.*

ARTICLE IN PRESS

AJKD

Original Investigation

Renin-Angiotensin System Inhibitors and Kidney and Cardiovascular Outcomes in Patients With CKD: A Bayesian Network Meta-analysis of Randomized Clinical Trials

Xinfang Xie, PhD,[1,] Youxia Liu, PhD,[1,*] Vlado Perkovic, MBBS,[2] Xiangling Li, MD,[3] Toshiharu Ninomiya, PhD,[2] Wanyin Hou, MD,[1] Na Zhao, PhD,[1] Lijun Liu, MD,[1] Jicheng Lv, MD,[1,2] Hong Zhang, MD, PhD,[1] and Haiyan Wang, MD, PhD[1,†]*

Background: There is much uncertainty regarding the relative effects of angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) in populations with chronic kidney disease (CKD).

Study Design: Systematic review and Bayesian network meta-analysis.

Setting & Population: Patients with CKD treated with renin-angiotensin system (RAS) inhibitors.

Selection Criteria for Studies: Randomized trials in patients with CKD treated with RAS inhibitors.

Predictor: ACE inhibitors and ARBs compared to each other and to placebo and active controls.

Outcome: Primary outcome was kidney failure; secondary outcomes were major cardiovascular events, all-cause death.

Results: 119 randomized controlled trials (n = 64,768) were included. ACE inhibitors and ARBs reduced the odds of kidney failure by 39% and 30% (ORs of 0.61 [95% credible interval, 0.47-0.79] and 0.70 [95% credible interval, 0.52-0.89]), respectively, compared to placebo, and by 35% and 25% (ORs of 0.65 [95% credible interval, 0.51-0.80] and 0.75 [95% credible interval, 0.54-0.97]), respectively, compared with other active controls, whereas other active controls did not show evidence of a significant effect on kidney failure. Both ACE inhibitors and ARBs produced odds reductions for major cardiovascular events (ORs of 0.82 [95% credible interval, 0.71-0.92] and 0.76 [95% credible interval, 0.62-0.89], respectively) versus placebo. Comparisons did not show significant effects on risk for cardiovascular death. ACE inhibitors but not ARBs significantly reduced the odds of all-cause death versus active controls (OR, 0.72; 95% credible interval, 0.53-0.92). Compared with ARBs, ACE inhibitors were consistently associated with higher probabilities of reducing kidney failure, cardiovascular death, or all-cause death.

Limitations: Trials with RAS inhibitor therapy were included; trials with direct comparisons of other active controls with placebo were not included.

Conclusions: Use of ACE inhibitors or ARBs in people with CKD reduces the risk for kidney failure and cardiovascular events. ACE inhibitors also reduced the risk for all-cause mortality and were possibly superior to ARBs for kidney failure, cardiovascular death, and all-cause mortality in patients with CKD, suggesting that they could be the first choice for treatment in this population.

Am J Kidney Dis. ■(■):■-■.

Table 1. Characteristics of Studies in Meta-analysis

Group	Mean Age, y	Mean Follow-up, y	No. of Trials and Participants	No. of Trials (Percentage of Patients), by Type				No. of Trials by CKD Definition[a]	No. of Trials by Proteinuria Class[b]
				DN Only	Mixed	Non-DN	Dialysis		
All trials	62.9	3.6	119 (n = 64,768)	54 (46.4)	35 (44.7)	30 (8.9)	13 (3.5)	GFR < 60: 29; proteinuria: 60; other: 30	A3: 50; A2: 21; A3: 5
ACEi vs placebo	62.4	4.0	34 (n = 21,491)	18 (51.8)	11 (45.1)	5 (3.1)	3 (2.2)	GFR < 60: 8; proteinuria: 22; other: 4	A3: 9; A2: 14; A3: 2
ARB vs placebo	62.2	3.3	7 (n = 4,854)	4 (65.6)	2 (32.2)	1 (2.2)	1 (1.7)	GFR < 60: 2; proteinuria: 5; other: 0	A3: 2; A2: 3; A1: 0
ACEi vs active control	63.2	3.7	38 (n = 10,628)	16 (19.1)	7 (58.8)	15 (22.9)	3 (2.4)	GFR < 60: 8; proteinuria: 17; other: 13	A3: 23; A2: 8; A1: 1
ARB vs active control	64.6	3.1	13 (n = 6,505)	3 (4.6)	4 (88.9)	3 (3.3)	3 (14.1)	GFR < 60: 6; proteinuria: 3; other: 4	A3: 1; A2: 3; A1: 0
ACEi vs ARB	49.6	4.0	8 (n = 1,141)	3 (33.0)	2 (36.8)	3 (30.1)	1 (5.3)	GFR < 60: 2; proteinuria: 3; other: 3	A3: 5; A2: 3; A1: 0
Dual blockade vs monotherapy	64.5	3.4	9 (n = 17,750)	4 (60.1)	2 (33.5)	2 (5.9)	1 (1.9)	GFR < 60: 2; proteinuria: 4; other: 3	A3: 4; A2: 2; A1: 2
3-arm study[c]	58.7	2.5	9 (n = 2,264)	6 (95.4)	0 (0)	2 (4.6)	1 (4.4)	GFR < 60: 1; proteinuria: 6; other: 1	A3: 4; A2: 2; A1: 0

Conclusion

- *This network meta-analysis provides evidence that ACE inhibitors are most likely to reduce the risk for kidney failure, cardiovascular events, and death in people with CKD and have superiority over ARBs and other classes of BP-lowering agents on renoprotective effects, as well as protection against death in the CKD population, so that these agents may be preferable in patients with CKD.*

We recommend **temporary discontinuation** of renal excreted drugs in people with a **GFR <60 ml/min/1.73** who have serious intercurrent illness that increases the risk of AKI.

These agents include, but are not limited to: RAAS blockers (including **ACE-Is, ARBs,** aldosterone inhibitors, direct renin inhibitors), diuretics, NSAIDs, metformin, lithium, and digoxin.

THANK YOU